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CALIFORNIA DEPARTMENT OF FOOD AND AGRICULTURE
SUMMARY OF TOXICOLOGICAL DATA
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

CYROMAZINE

SB 950-XXX, Tolerance # 414

August 8, 1986

I. DATA GAP STATUS

Combined Rat: No data gap, possible adverse effect.
(Chronic + Onco)

Chronic dog: Data gap, only 6 month study--not chronic.

Onco mouse: No data gap, possible adverse effect.

Repro rat: No data gap, no adverse effect.

Terato rat: Data gap, inadequate study, no adverse effect indicated.

Terato rabbit: No data gap, possible adverse effect.

Gene mutation: Data gap, no study on file.

Chromosome: Data gap, inadequate study, no adverse effect indicated.

DNA damage: Data gap, no study on file.

Neurotox: Not required.

Note, Toxicology one-liners are attached

** indicates acceptable study
Bold face indicates possible adverse effect
File name 1c:cyromazi

SB950-
TOLERANCE #414

CHRONIC, DOG

008 902743-5 only a subchronic(6 month) study - not reviewed for SB950

COMBINATION, RAT

**** 001-4 902751-4** (6/30/82, IRDC) FM, 5/13/86 Cyromazine technical, 95.5% and 95.3% pure; 3000, 300, 30 or 0 ppm in the feed; NOEL = 300 ppm, significant increase intesticular interstitial cell tumors and female mammary adenomas/carcinomas at 3000 ppm; report and study acceptable.

020 902761 Addendum to 902751-4, 12 month interim report

020 902762 Addendum to 902751-4, 12 month interim histopath

ONCOGENICITY, MOUSE

018 902748 Addendum to 902749, pilot study

**** 004-7 902749-50, 902755-7** (6/30/82, IRDC) FM, 5/13/86 Cyromazine technical, 95.3% & 95.5% pure; 3000, 1000, 50 or 0 ppm in the feed; NOEL= 50 ppm; significant increase in malignant lymhomas in 3000 ppm males, trend for increase in 1000 ppm males; report and study acceptable.

019 902759 Addendum to 902749 12 month interim report

019 902760 Addendum to 902749 12 month interim histopath

REPRODUCTION, RAT

** 017-18 902766-7 (12/1981, IRDC) JAP Acceptable with no adverse effects.
Cyromazine technical, 0, 30, 1000 or 3000 ppm; NOEL for parental (systemic effects) = 30 ppm; NOEL for reproductive effects = 100 ppm (F_1 @ 3000 slight decrease # pups from live, F_0 and F_1 pup weight decrease)

TERATOLOGY, RAT

017/53 36220 Addendum, pilot study to 36221

053 36221 (12/1979, IRDC) JAP, 10/25/85 Unacceptable with no teratogenic effect observed. CGA 72662 technical (96.3% purity); 25/group were given 0, 100, 300 and 600 mg/kg/day on days 6-19 by oral gavage; this rat teratology study shows maternal and fetal toxicity at 300 and 1000 mg/kg/day. NOEL is 100 mg/kg/day. Upgradeable

1C CYROMAZINE
TERATOLOGY, RABBIT

017 902764 Addendum, pilot to 902765

017 902765 (IRDC, 1981) JAP 6/16/86 CGA-72662 technical
4.

0, 10, 25, 30, 50, 60 & 75 mg/kg/day by gavage 6-27, Dutch Belted Rabbits. Maternal NOEL = 10 mg/kg (weight gain); developmental NOEL < 10 mg/kg (embryo fetotoxicity). Incomplete, unacceptable, with possible adverse effects noted.

028 22095 Addendum to 902765, Individual clinical observations JAP 10/85

028 22096 Addendum to 902765, Individual fetal variations JAP 10/85

028 22097 Addendum to 902765, Individual uterine parameters for females that died, aborted or were killed JAP 10/85

028 22098 Addendum to 902765, Historical control values JAP 10/85

028 22099 Addendum to 902765, Statistical analysis of skeletal variants by IRDC. Analyzed 13 ribs and 27 pre-sacral vertebrae, not significant at 10 mg/kg/day,(low dose). Note, EPA statistical analysis disagrees, see Vol.056 #43730. JAP 10/85

028 22101 Addendum to 902765 JAP 10/85 Acclimatization history and health of animals - experiments I and II.

028 22100 Addendum to 902765 JAP 10/85 Summary by Ciba Geigy and reviews by Drs. Beaudoin, Holson, Harris and Johnson. Duplicate of IRDC statistical review. Peer review by consultants all agree that a NOEL for maternal and developmental toxicity was established at 10 mg/kg/day. Copy of EPA electronic letter to Ciba Geigy, 7-3-84, study as inadequate due to poor health, "erratic" weight gain, and "mishandling" of animals. (Note,

consultants reviews were previously reviewed by C.S.K. on 9-24-84 as record number 13563).

056 43730 Addendum to 902765, reviewed by JAP 5-23-86, no worksheet. EPA's comments, 12-13-84, on Ciba-Geigy' response to EPA review of IRDC study. EPA used incorrect method to determine pre-implantation loss and as implantation occurs prior to initiation of dosing, this should not be affected by dosing. JAP disagrees with EPA's statement that there was mishandling of animals. One intubation death is not evidence for this. EPA stated concern over the incidence in all treated groups of 13 ribs and 27 presacral vertebrae. As these findings usually occur together (when there are extra ribs, there are extra vertebrae) only 1 should be of concern. EPA concludes that there was no NOEL established for fetal toxicity and that the maternal NOEL was 10 mg/kg/day.

1C CYROMAZINE

** **034 31090** (1985, WIL) JAP 10-85 and 6-18-86. Teratology, NZW rabbit, WIL Laboratory, 1-23-85, Vehicle control, untreated control, 5, 10, 30 and 60 mg/kg/day by gavage days 7-19. Maternal NOEL = 10 mg/kg/day (Reduced body weight gain), Developmental NOEL = 5 mg/kg/day (Resorptions and terata). EPA classified as minimum with the above NOELs. Acceptable, adverse effect as determined by EPA.

056 38377 Addendum to 31090 JAP 5/23/86, no worksheet. EPA letter, 5-2-85, study remains classified as Core Minimum with maternal NOEL=10 and developmental NOEL=5.EPA letter, 4-14-85, EPA comments on Ciba-Geigy response to EPA review. Peer Review by C.Kimmel, EPA, 4-5-85. Concludes maternal NOEL = 10 mg/kg/day and since some malformations seen at 10 and there were few fetuses to evaluate, fetal NOEL is 5 mg/kg/day. EPA review, 2-5-85, which lists problems with study including low pregnancy rate at 10mg/kg and low values for implantation sites, both of these events occur prior to dosing. They also mention 1 fetus at 10 and 1 fetus at 30 that had cyclopia. These are considered by EPA to be evidence of a teratogenic effect of the compound even though this was not seen at 60 mg.

057 38378 Addendum to 31090, JAP 5/23/86, no worksheet. Ciba-Geigy response to EPA review dated 2/27/85. Letter from WIL, 3/4/85, addressing pregnancy rate, weight range and historical data. Letter from Wil, 1/28/85, with historical control. WIL suggests cyclopia may be of genetic origin in rabbits from Buckshire. Letter from WIL, 2-14-85, which correlated malebreeder with fetal malformations observed. This is not the best way to present data as it appears that male #2749 contributes most of the malformed fetuses. However #2749 sired 58% of the fetuses in this study and therefore would be expected to sire most of the malformed fetuses.

At EPA’s request, a repeat study using NZW rabbits from Hazleton- Dutchland, is being conducted at WIL. This study will investigate male # 2749 as being the genetic source of the previously observed cyclopia as well as evaluating

25 litters/dose level at 0, 5, 10, and 30 mg/kg/day. There will also be a 25 litter post-natal phase to this study. This study was due at CDFA 12-85. This study should answer any questions about the potential developmental toxicity of cyromazine.

1C CYROMAZINE

MUTAGENICITY STUDIES

MUTA 842 GNMU No study on file

MUTA 843 CHROMOSOMES

018 902768 Mouse dominant lethal. (1981, Ciba-Geigy) JRG 3/13/86 Cyromazine, batch P_3; 20 males/group were given 0, 326 or 678 mg/kg by oral gavage once and mated for 6 consecutive weekly periods with 40 females (34 for high dose - 3 males died). No evidence of dominant lethal effect is

reported. Incomplete (missing info), Unacceptable (no positive control. Not upgradeable

018 902769 Hamster micronucleus test. (1980, Ciba-Geigy) JRG 3/13/86 Cyromazine, 98.9%; 6/sex/group were given 2X 0, 2000, 4000 or 8000 mg/kg by oral gavage and sacrificed at 24 hours; 1000 marrow cells of 3/sex/group were analyzed; no evidence of clinical toxicity or micronuclei formation is reported. Incomplete (missing data), unacceptable (protocol). Not upgradeable